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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/764,420	LUM ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *5-7,10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9 and 12-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I and Species D and G in the reply filed on 26 May 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5-7 and 10-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 26 May 2006.

It is also acknowledged that applicant canceled claims 34-67 in their response of 26 May 2006.

Applicant's election with traverse of the sequence election in claim 33 in the reply filed on 26 May 2006 is acknowledged. The traversal is on the ground(s) that a combination of sequences can be examined in addition to a single sequence. This is found persuasive and currently amended claim 33 is examined on the merits as it stands.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

In regards to claims 1-32, the instant claims are drawn to a toxicological algorithm. A toxicological algorithm is non-statutory unless the claims include a step of physical transformation, or if the claims include a useful, tangible and concrete result. It is important to note, that the claims themselves must include a physical transformation step or a useful, tangible and concrete result in order for the claimed invention to be statutory. It is not sufficient that a physical transformation step or a useful, tangible, and concrete result be asserted in the specification for the claims to be statutory. In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, tangible, and concrete result.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-32 do not produce a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the method is

outputted to a display or a memory or another computer on a network, or by including a physical transformation.

As stated in section 2106 of the M.P.E.P., "The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a Sec. 101 judicial exception, in that the process claim must set forth a practical application of that Sec. 101 judicial exception to produce a real-world result. Benson, 409 U.S. at 71-72, 175 USPQ at 676-77 (invention ineligible because had "no substantial practical application."). "[A]n application of a law of nature or mathematical formula to a . . . process may well be deserving of patent protection." Diehr, 450 U.S. at 187, 209 USPQ at 8 (emphasis added); see also Corning, 56 U.S. (15 How.) at 268, 14 L.Ed. 683 ("It is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted . . ."). In other words, the opposite meaning of "tangible" is "abstract.""

Claim 33 is rejected because the product mentioned (the "population of oligonucleotide probes") is natural and lacks the hand of man. This rejection could be remedied by indicating that the "population of oligonucleotide probes" is isolated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 12-16, 18-26, 28, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Castle et al. [WO 02/059560 A2].

Claims 1-4, 12-16, 18-26, 28, and 30-32 state:

1. A method for determining whether an agent possesses a defined biological activity, the method comprising the steps of: (a) making at least one comparison from the group consisting of: (1) comparing an efficacy value of the agent to at least one reference efficacy value to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins; (2) comparing a toxicity value of the agent to at least one reference toxicity value to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (3) comparing a classifier value of the agent to at least one reference classifier value to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (b) using the comparison result(s) obtained in step (a) to determine whether the agent possesses the defined biological activity.

2. The method of claim 1 comprising the steps of: (a) making at least two comparisons from the group consisting of: (1) comparing an efficacy value of the agent to at least one reference efficacy value to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins; (2) comparing a toxicity value of the agent to at least one reference toxicity value to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (3) comparing a classifier value of the agent to at least one reference classifier value to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (b) using the comparison results obtained in step (a) to determine whether the agent possesses the defined biological activity.

3. The method of claim 1 comprising the steps of: (a) comparing an efficacy value of the

agent to at least one reference efficacy value to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins; (b) comparing a toxicity value of the agent to at least one reference toxicity value to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (c) comparing a classifier value of the agent to at least one reference classifier value to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (d) using the efficacy comparison result, the toxicity comparison result and the classifier comparison result to determine whether the agent possesses the defined biological activity, wherein steps (a), (b) and (c) can occur in any order with respect to each other.

4. The method of claim 1 wherein the agent is a chemical agent.

12. The method of claim 1 wherein the at least one reference classifier value is the classifier value of a reference agent that possesses the defined biological activity.

13. The method of claim 1 wherein at least one member of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent is calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

14. The method of claim 13 wherein at least two members of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent are calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

15. The method of claim 13 wherein the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent are calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

16. The method of claim 13 wherein the living cells are selected from the group consisting of heart cells, liver cells and adipocyte cells.

18. The method of claim 1 wherein the defined biological activity is the ability to affect a biological process in vivo, and wherein at least one member of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent is calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

19. The method of claim 18 wherein the biological process is an acute or chronic disease in a mammal.

20. The method of claim 1 wherein the defined biological activity is the ability to affect a biological process in vivo, and wherein at least two members of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent are calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

21. The method of claim 20 wherein the biological process is an acute or chronic disease in a mammal.

22. The method of claim 1 wherein the defined biological activity is the ability to affect a biological process in vivo, and wherein the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent are calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

23. The method of claim 22 wherein the biological process is an acute or chronic disease in a mammal.

24. The method of claim 1 wherein the defined biological activity is the ability to affect a biological process in a first living tissue, and wherein at least one member of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent is calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in a second living tissue, wherein the first living tissue is a different type of tissue than the second living tissue.

25. The method of claim 1 wherein the defined biological activity is the ability to affect a biological process in a first living tissue, and wherein at least two members of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent are calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in a second living tissue, wherein the first living tissue is a different type of tissue from the second living tissue.

26. The method of claim 1 wherein the defined biological activity is the ability to affect a biological process in a first living tissue, and wherein the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent are calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in a second living tissue, wherein the first living tissue is a different type of tissue than the second living tissue.

28. The method of claim 1 wherein at least one member of the group consisting of the toxicity-related population of genes and the toxicity-related population of proteins yields at least one toxicity-related gene expression pattern, or toxicity-related protein expression pattern, in response to the agent, that correlates with the presence of at least one undesirable biological response caused by the agent in a living thing, wherein the at least one toxicity-related gene expression pattern, or at least one toxicity-related protein expression pattern, appears before the undesirable biological response.

30. The method of claim 1 comprising the steps of: (a) making at least one comparison from the group consisting of: (1) comparing an efficacy value of the agent to a scale of efficacy values to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins; (2) comparing a toxicity value of the agent to a scale of toxicity values to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (3) comparing a classifier value of the agent to a scale of classifier values to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (b) using the comparison result(s) obtained in step (a) to determine whether the agent possesses the defined biological activity.

31. The method of claim 30 comprising the steps of: (a) making at least two comparisons from the group consisting of: (1) comparing an efficacy value of the agent to a scale of efficacy values to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins; (2) comparing a toxicity value of the agent to a scale of toxicity values to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (3) comparing a classifier value of the agent to a scale of classifier values to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (b) using the comparison results obtained in step (a) to determine whether the agent possesses the defined biological activity.

32. The method of claim 30 comprising the steps of: (a) comparing an efficacy value of the agent to a scale of efficacy values to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-

related population of proteins; (b) comparing a toxicity value of the agent to a scale of toxicity values to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (c) comparing a classifier value of the agent to a scale of classifier values to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (d) using the efficacy comparison result, the toxicity comparison result and the classifier comparison result to determine whether the agent possesses the defined biological activity, wherein steps (a), (b) and (c) can occur in any order with respect to each other.

The document of Castle et al., entitled, "A method and system for predicting the biological activity, including toxicology and toxicity, of substances," states in the abstract:

> A method for assessing toxicity and toxicology of a substance is disclosed comprising: exposing a set of at least two genes to the substance; monitoring the response of each gene in the set of genes to the substances; analyzing the variance of the response to the substance for each gene using contrast analysis; constructing a summary score for each gene in the set of genes; performing a logistic regression analysis upon the summary scores; and using the results of the logistic regression analysis to provide a predictive model regarding the toxicity and toxicology of the substance.

The algorithm of interest is elaborated on pages 32-33 of Castle et al., which states:

> The following is a model developed from gene expression of rat livers using Affymetrix RU35 Rat Chip data. The rats were either treated with a toxic dose, non-toxic dose or vehicle controls. The raw expression data expressed as normalized average differences were then entered into the model described here.
>
> In achieving this analysis, a preferred expression similarity profiling for predictive toxicology algorithm is employed. In this algorithm, let Xij represent gene expression values for the i'th gene and j'th sample (I = 1 to I, j = 1 to J). Let Yj, Dj, and Tj represent the indicator of toxicity for the j'th sample, the dose for the j'th sample, and the time for the j'th sample, respectively. In the first step, time stable and dose dependent patterns are selected. For gene i,fit a two-factor analysis of variance model. This model can be expressed as
>
> Xij = a+b*Dj+c*Tj+d*Dj*Tj
>
> for the case of two dose groups (Dj = 0 or 1) and two time points (Tj = 0 or 1). In this model, the parameters (a, b, c, d) are estimated via a least squares algorithm.
> Accomodating additional time/dose levels is accomplished by adding additional model parameters for each additional time and/or dose level. For example, the case of four time points (Tj = 0 or 1 or 2 or 3) and three dose groups (Dj = 0 or 1 or 2 can be expressed as:

> Xij = a+B1*D1j+b2*D2j+c1*T1j+c2*t2j+c3*t3j+d1*D1j*T1j+ d2*D1j*T2j+ d3*D1j*T3j+ d4*D2j*T1j+d5*D1j*T2j+d6*D2j*T3j
> Where T1j = 1 if Tj = 1, T2j = 1 if Tj = 2, etc. The parameters (a, b1, b2, c1, c2, c3, d1, d2, d3, d4, d5, d6) are estimated as above.

Consequently, Castle et al. use linear regression to compare the reference toxicity of a substance (toxicity of a chemical agent at an initial time) to toxicity as time progresses. Although this passage describes nominally a toxicological algorithm, the actual algorithm itself is not limited to toxicology. As stated in page 8, line 10-17:

> An aspect of the present invention is an analysis of the variance for each gene contrast analysis. In this gene contrast analysis, the response of a gene or set of genes is monitored upon exposure to a chemical. In one preferred embodiment, the response of a gene or set of genes to a chemical can be fitted into one of four patterns illustrated in Figures 1a, 1b, 1c, and 1d. In this preferred embodiment, upon classification into one of these four groups, an analysis is then performed which categorizes the gene contrast analysis as one of four summary scores...

Figure 1 of Castle et al. is interpreted to illustrate a) efficacy, b) toxicity, c) no effect, or d) plateau effect of the agent. The model of Castle et al. is used not only to determine agent toxicity, but also agent efficacy, by assigning the agent a classification such as that shown in Figure 1 of Castle et al. The reference value is interpreted to be the effect of the agent at an initial time on the set of genes while the actual value is interpreted to be the efficacy, toxicity, or classification of the agent at the final time examined. The effect on gene expression caused by the agent determines the classification of biological activity of the agent. The instant disclosure does not limit the relation between the reference and actual agents to possess a specific relationship in time (i.e. the reference and actual samples are interpreted to occur at different times on the same tissue sample).

The analysis completed is Castle et al. in completed on a chip *in vitro* on rat liver cells to analyze gene expression related to disease. The purpose of the study of Castle

et al. is to predict the effect of substances *in vivo* as a result of *in vitro* experimentation. Castle et al. use a plurality of different tissue samples in the Affymetrix gene chip to complete the analysis (there are a plurality of tissue samples or "j's" in the equations listed). Each tissue sample affects the linear regression analysis (i.e. calculations) of the equations cited above in Castle et al. Each tissue sample "j" is interpreted to be its own tissue type, wherein each tissue type affects one another in the computation of agent efficacy or toxicity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 9, 13, 16-17, 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Castle et al. in view of Mukherjee et al. [Molecular Endocrinology, 2000, volume 14, pages 1425-1433].

Claims 1, 8, 9, 13, 16-17, 27 and 29 state:

1. A method for determining whether an agent possesses a defined biological activity, the method comprising the steps of: (a) making at least one comparison from the group consisting of: (1) comparing an efficacy value of the agent to at least one reference efficacy value to yield an efficacy comparison result, wherein each efficacy value represents at least one expression pattern of the same efficacy-related population of genes, or at least one expression pattern of the same efficacy-related population of proteins; (2) comparing a toxicity value of the agent to at least one reference toxicity value to yield a toxicity comparison result, wherein each toxicity value represents at least one expression pattern of the same toxicity-related population of genes, or at least one expression pattern of the same toxicity-related population of proteins; (3) comparing a classifier value of the agent to at least one reference classifier value to yield a classifier comparison result, wherein each classifier value represents at least one expression pattern of the same classifier population of genes, or at least one expression pattern of the same classifier population of proteins; and (b) using the comparison result(s) obtained in step (a) to determine whether the agent possesses the defined biological activity.

8. The method of claim 1 wherein the defined biological activity is partial agonist activity with respect to a biological response, or with respect to a protein that mediates a biological response.

9. The method of claim 8 wherein the defined biological activity is partial agonist activity with respect to PPAR.gamma.

13. The method of claim 1 wherein at least one member of the group consisting of the efficacy value of the agent, the toxicity value of the agent and the classifier value of the agent is calculated from at least one member of the group consisting of gene expression levels and protein expression levels measured in living cells cultured in vitro.

16. The method of claim 13 wherein the living cells are selected from the group consisting of heart cells, liver cells and adipocyte cells.

17. The method of claim 16 wherein the living cells are 3T3L1 adipocyte cells.

27. The method of claim 1 wherein at least one member of the group consisting of the efficacy-related population of genes and the efficacy-related population of proteins

yields at least one efficacy-related gene expression pattern, or efficacy-related protein expression pattern, in response to the agent, that correlates with the presence of at least one desired biological response caused by the agent in a living thing, wherein the at least one efficacy-related gene expression pattern, or at least one efficacy-related protein expression pattern, appears before the desired biological response.

29. The method of claim 1 wherein (1) at least one member of the group consisting of the efficacy-related population of genes and the efficacy-related population of proteins yields at least one efficacy-related gene expression pattern, or efficacy-related protein expression pattern, in response to the agent, that correlates with the presence of at least one desired biological response caused by the agent in a living thing, wherein the at least one efficacy-related gene expression pattern, or at least one efficacy-related protein expression pattern, appears before the desired biological response; and (2) at least one member of the group consisting of the toxicity-related population of genes and the toxicity-related population of proteins yields at least one toxicity-related gene expression pattern, or at least one toxicity-related protein expression pattern, in response to the agent, that correlates with the presence of at least one undesirable biological response caused by the agent in a living thing, wherein the at least one toxicity-related gene expression pattern, or at least one toxicity-related protein expression pattern, appears before the undesirable biological response.

The document of Castle et al., entitled, "A method and system for predicting the biological activity, including toxicology and toxicity, of substances," states in the abstract:

> A method for assessing toxicity and toxicology of a substance is disclosed comprising: exposing a set of at least two genes to the substance; monitoring the response of each gene in the set of genes to the substances; analyzing the variance of the response to the substance for each gene using contrast analysis; constructing a summary score for each gene in the set of genes; performing a logistic regression analysis upon the summary scores; and using the results of the logistic regression analysis to provide a predictive model regarding the toxicity and toxicology of the substance.

The algorithm of interest is elaborated on pages 32-33 of Castle et al., which states:

> The following is a model developed from gene expression of rat livers using Affymetrix RU35 Rat Chip data. The rats were either treated with a toxic dose, non-toxic dose or vehicle controls. The raw expression data expressed as normalized average differences were then entered into the model described here.

> In achieving this analysis, a preferred expression similarity profiling for predictive toxicology algorithm is employed. In this algorithm, let Xij represent gene expression values for the i'th gene and j'th sample (I = 1 to I, j = 1 to J). Let Yj, Dj, and Tj represent the indicator of toxicity for the j'th sample, the dose for the j'th sample, and the time for the j'th sample, respectively. In the first step, time stable and dose dependent patterns are selected. For gene i,fit a two-factor analysis of variance model. This model can be expressed as
>
> Xij = a+b*Dj+c*Tj+d*Dj*Tj
>
> for the case of two dose groups (Dj = 0 or 1) and two time points (Tj = 0 or 1). In this model, the parameters (a, b, c, d) are estimated via a least squares algorithm.
> Accomodating additional time/dose levels is accomplished by adding additional model parameters for each additional time and/or dose level. For example, the case of four time points (Tj = 0 or 1 or 2 or 3) and three dose groups (Dj = 0 or 1 or 2 can be expressed as:
>
> Xij = a+B1*D1j+b2*D2j+c1*T1j+c2*t2j+c3*t3j+d1*D1j*T1j+ d2*D1j*T2j+ d3*D1j*T3j+ d4*D2j*T1j+d5*D1j*T2j+d6*D2j*T3j
>
> Where T1j = 1 if Tj = 1, T2j = 1 if Tj = 2, etc. The parameters (a, b1, b2, c1, c2, c3, d1, d2, d3, d4, d5, d6) are estimated as above.

Consequently, Castle et al. use linear regression to compare the reference toxicity of a substance (toxicity of a chemical agent at an initial time) to toxicity as time progresses. Although this passage describes nominally a toxicological algorithm, the actual algorithm itself is not limited to toxicology. As stated in page 8, line 10-17:

> An aspect of the present invention is an analysis of the variance for each gene contrast analysis. In this gene contrast analysis, the response of a gene or set of genes is monitored upon exposure to a chemical. In one preferred embodiment, the response of a gene or set of genes to a chemical can be fitted into one of four patterns illustrated in Figures 1a, 1b, 1c, and 1d. In this preferred embodiment, upon classification into one of these four groups, an analysis is then performed which categorizes the gene contrast analysis as one of four summary scores...

Figure 1 of Castle et al. is interpreted to illustrate a) efficacy, b) toxicity, c) no effect, or d) plateau effect of the agent. The model of Castle et al. is used not only to determine agent toxicity, but also agent efficacy, by assigning the agent a classification such as that shown in Figure 1 of Castle et al. The reference value is interpreted to be the effect of the agent at an initial time on the set of genes while the actual value is interpreted to be the efficacy, toxicity, or classification of the agent at the final time examined. The effect on gene expression caused by the agent determines the classification of biological activity of the agent. The instant disclosure does not limit the

relation between the reference and actual agents to possess a specific relationship in time (i.e. the reference and actual samples are interpreted to occur at different times on the same tissue sample).

The analysis completed in Castle et al. is completed on a chip *in vitro* on rat liver cells to analyze gene expression related to disease. The purpose of the study of Castle et al. is to predict the effect of substances *in vivo* as a result of *in vitro* experimentation. Castle et al. use a plurality of different tissue samples in the Affymetrix gene chip to complete the analysis (there are a plurality of tissue samples or "j's" in the equations listed). Each tissue sample affects the linear regression analysis (i.e. calculations) of the equations cited above in Castle et al. Each tissue sample "j" is interpreted to be its own tissue type, wherein each tissue type affects one another in the computation of agent efficacy or toxicity.

Castle et al. does not teach partial agonist activity with respect to a biological response, partial agonist activity with respect to PPARγ, use of 3T3L1 adipocyte cells, or production of an efficacy related gene pattern.

The article of Mukherjee et al., entitled, "A selective peroxisome prolierator-activated receptor-γ (PPARγ) modulator blocks adipocyte differentiation but stimulates glucose uptake in 3T3-L1 adipocytes," states in the abstract:

> Peroxisome proliferator-activated receptor-γ (PPARγ) agonists such as the thiazolidinediones are insulin sensitizers used in the treatment of type 2 diabetes. These compounds induce adipogenesis in cell culture models and increase weight gain in rodents and humans. We have identified a novel PPARγ ligand, LG100641, that does not activate PPARγ but selectively and competitively blocks thiazolidinedione-induced PPARγ activation and adipocyte conversion. It also antagonizes target gene activation as well as repression in agonist-treated 3T3-L1 adipocytes.

The first paragraph in the introduction of Mukherjee et al. elaborates on the scope and purpose of the study:

> Peroxisome proliferator-activated receptor-γ (PPARγ) is a member of the intracellular receptor family of transcription factors... PPARγ) is expressed at high levels in fat, spleen, and colon but is also detectable in skeletal muscle, liver and other tissues... Interest in this receptor increased when it was clear that insulin sensitizers of the thiazolidinedione class [troglitazone, rosiglitazone (BRL 49653), Pioglitazone], are high-affinity ligands for PPARγ. A correlation was reported between the affinity of thiazolidinediones for PPARγ and the minimum effective dose required to lower glucose levels in diabetic rodent models.

Consequently, there is a correlation between PPARγ affinity and the lowering of glucose in diabetic rodent models.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the toxicological algorithm of Castle et al. to determine and classify the activity of an agent by use of the PPARγ efficacy analysis of Mukherjee et al. because while both studies examine rodent cells, Mukherjee et al. has the advantage of exemplifying a correlation of the relations between the required agents, cell species, and the efficacy in treating diabetes related complications. The study of Mukherjee et al. is an application of the patent of Castle et al. to diabetes related drugs with the advantage of treating diabetic related complications.

Conclusion

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Andrew Wang, Supervisory Patent Examiner, can be reached at (571) 272-0811.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
8 January 2007

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